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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,440	LANE, DAVID PHILIP	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 8, 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include species not previously examined.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

Applicant amends claim 1 to introduce a species not previously examined, and cancels claims 4-7, 9-10, 12-27.

Accordingly, claims 1-3, 8, 11, SEQ ID NO:4, disrupting the binding of p53 and mdm2, are being examined.

The following are the remaining rejections.

SEQUENCE RULE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

The sequences recited in the specification, for example, the peptides TIP and TIP12/1 recited in figure 1 legend on page 5 are not accompanied by sequence identification numbers.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claim 8 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

The limitation of "the agent has the property of competing with mdm2 for binding p53, but does not inhibit the ability of p53 to induce cell cycle arrest or apoptosis in cells after DNA damage" claimed in Claim 8 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for "competing with mdm2 for binding p53, but does not inhibit the biological activity of p53, e.g. the DNA specific binding of p53 (p.10, lines 31-34), and "inhibitors of the p53-mdm2 interaction do not interfere with the capacity of p53 to interact with the transcription apparatus". There is however no mention of does not inhibit the ability of p53 to induce cell cycle arrest or apoptosis in cells after DNA damage".

The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 1-3, 8, 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for increasing the level of p53 protein in breast cancer cells that do not overexpress mdm2, comprising administering the peptide consisting of SEQ ID NO:3, inserted in thioredoxin, does not reasonably provide enablement for an in vitro method for inducing growth inhibition or apoptosis in

a population of "cancer cells in which mdm2 is not overexpressed", comprising administering an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif "FXaaXaaXaaW (SEQ ID NO:4)", wherein said agent has the property of disrupting the binding of p53 and mdm2, or wherein said agent could comprise a peptide having an amino acid sequence that consists of "a portion of human p53 which have the property of binding to mdm2", or wherein said agent could comprise a peptide at least 70% amino acid sequence identity with "a portion of human p53". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-3, 8, 11 are drawn to :

An in vitro method for inducing growth inhibition or apoptosis in a population of cancer cells in which mdm2 is not overexpressed, comprising administering an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif "**F**XaaXaaXaa**W** (SEQ ID NO:4)", wherein Xaa is any amino acid, and wherein said agent has the property of disrupting the binding of p53 and mdm2 (claim 1).

The method of claim 1, wherein the p53 is activated for DNA specific binding and transcription (claim 2).

The method of claim 1, wherein said agent could comprise a peptide having an amino acid sequence that consists of a portion of human p53 which have the property of binding to mdm2 (claim 3).

The method of claim 1, wherein the agent has the property of competing with mdm2 for binding p53, but does not inhibit the ability of p53 to induce cell cycle arrest or apoptosis in cells after DNA damage (claim 8).

The method of claim 1, comprising administering an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif FXaaXaaXaaW (SEQ ID NO:4), wherein the peptide has at least 70% amino acid sequence identity with a portion of human p53 (claim 11).

The specification discloses the wild type p53 peptide of SEQ ID NO:2 (TIP) and a synthetic variant, SEQ ID NO:3 (TIP 12/1), that are inserted into thioredoxin, wherein TIP wt contains the sequence corresponding to p53 wild type sequence P13 to N29. The specification discloses that TIP and TIP12/1 are inhibitors of the interaction between p53 and mdm2, as compared to the control thioredoxin lacking the peptide insertion (p. 24-25 and figure 1). The specification discloses that however **TIP is 20 times less potent than TIP 12/1 in inhibition of said interaction between p53 and mdm2**, and that this has to be attributed to the 50 times less potent achieved by the wt peptide when compared with the peptide 12/1 competition in in vitro assay by phage display taught in Bottger et al, 1997 (p. 25, item 2). The specification further discloses that TIP 12/1 exhibits strong enough inhibitory potential to compete against endogenous level of wt53 in tumor cells for binding to mdm2 (p.25, lines 31-33). The specification discloses that in in vitro assay using ELISA plates, TIPwt has inhibitory IC50 of 15000 nM, as compared to 300 nM for TIP 12/1, and 400nM for full length p53 (table 1 on page 35) .

The specification discloses that microinjection of a plasmid containing TIP12/1 (SEQ ID NO:3) into T22, a mouse prostate derived cell, having low level of p53 and mdm2 and transfected with p53 responsive beta-galactosidase reporter, strongly induces the p53 dependent reporter activity (p.27), as compared to a lower level of galactosidase activity with the wild type TIP (p.27) .The specification further discloses co-transfection of a plamid containing said reporter, and a plasmid containing TIP12/1 (SEQ ID NO:3) into three different cell lines: 1) a breast cancer cell line MCF-7 which expresses low level of wt p53 and no reported mdm2 elevation (p.28, lines 5-7, and last paragraph), 2) an osteosarcoma cell line U2-OS, which expresses elevated levels of mdm2-mRNA, but without gene amplification for mdm2, and 3) a human osteosarcoma cell OSA, with elevated levels of mdm2 due to gene amplification for mdm2 (p.28, first, and last paragraph). The specification discloses that induction of p53 transcriptional activity is the highest, comparable with induction by UV, for the breast cancer cell line having undetectable levels of mdm2, as compared to the other two cell lines with elevated levels of mdm2 (p29 and figure 3). The specification discloses that the protein level of p53 is also increased in T22 cells transfected with TIP 12/1 (p.30).

It is noted that although T22, a mouse prostate derived cell, having low level of p53 and mdm2, shows an increased level of p53 when transfected with TIP12/1 (p.30, first paragraph), there is however no indication that the transfected cells have apoptosis, or cell death, because otherwise they would not be available for testing the level of p53 protein.

It is further noted that a peptide, less than 25 amino acids in length, and including the peptide motif "**F**XaaXaaXaa**W** (SEQ ID NO:4)", wherein Xaa is any amino acid of claims 1-2, 8 and 11, encompasses a peptide of any length from 5 to 25 amino acids comprising the motif "FXaaXaaXaaW (SEQ ID NO:4)", wherein Xaa is any amino acid, wherein said peptide could be a variant of SEQ ID NO:3 of the claimed invention or the wild type p53 peptide of SEQ ID NO:2.

It is further noted that a peptide having an amino acid sequence that consists of a portion of human p53 which have the property of binding to mdm2 of claim 3 encompasses the wild type p53 peptide of SEQ ID NO:2.

1. One cannot extrapolate the teaching in the specification to the scope of the claims. **It is unpredictable that a peptide of less than 25 amino acids in length, and comprising the motif "FXaaXaaXaaW (SEQ ID NO:4)", wherein Xaa is any amino acid, could adequately increase the p53 activity, and consequently growth inhibition or apoptosis in a cancer cell in which mdm2 is not overexpressed**, in view of the following teaching in the art.

Bottger V at al, Oncogene, 1996, 13: 2141-2147, IDS# 5 submitted on 09/06/2000 teach that specific activity of various synthetic peptides, having the common motif "**F**XaaXaaXaa**W,** as inhibitors of the hdm2-p53 interaction **varies over 100 fold** range (p.2144, first column, first paragraph, table 1 on page 2142, and figure 5 on page 2144). Bottger et al further teach that phage clone 12/1 (the sequence 12/1 on table 1 on page 2142), the most potent inhibitor, contains the motif PX**F**XDY**W**XXL, wherein **each of the selected consensus residue is important for the maximum strength of**

interaction with hdm2 (p.2144, first column, first paragraph). Bottger V at al further teach that the **L** of the wt p53 sequence TFSDL**W** is important for hdm2 binding and that the Tyrosine (Y), not found in the wild type, is selected over the wild type L in phage display increases the inhibitory activity, probably as additional binding points for hdm2, for improved stability of the peptide or its better conformational fit into the hdm2 binding pocket (p.2144, second column, third paragraph).

Thus based on the teaching in the specification, and by the art, except for TIP12/1 comprising SEQ ID NO:3 inserted in thioredoxin, or the motif PX**F**XDY**W**XXL, one cannot predict that any other peptides sharing the motif **F**XaaXaaXaa**W**, including the wt p53 peptide of SEQ ID NO:2, would have adequate strength of interaction with hdm2 to displace an adequate numbers of the wild type full length, endogenous p53 molecules from binding to hdm2, such that the activity of p53 is adequately induced, resulting in growth inhibition or apoptosis, because of the following reasons:

a) The activity of the synthetic peptides sharing the motif **F**XaaXaaXaa**W** (SEQ ID NO:4) could have an inhibitory activity difference as much as over 100 fold-range (see table 1, phages 12/1-5, on page 2142, and p.2144, first column, first paragraph in Bottger et al), and

b) The wild type full length p53 has an inhibitory value IC50 of 400 nM, versus an IC50 of 300 nM for the most potent inhibitor, TIP12/1, whereas even the wild type p53 peptide sequence of SEQ ID NO:2 (TIP) has only an IC50 of 15000 nM, as disclosed in the specification.

In other words, In view of the strong inhibitory value of wild type full length p53 as compared to that of even the most potent inhibitor, TIP 12/1, one cannot predict that other claimed peptides sharing the motif **F**XaaXaaXaa**W** (SEQ ID NO:4) would have an adequate inhibitory activity to displace an adequate number of the wild type full length endogenous p53 molecules from binding to mdm2, such that the activity of p53 is adequately induced, resulting in growth inhibition or apoptosis.

Further one cannot predict that the claimed peptide of any length provided it is of less than 25 amino acids in length, and comprising the motif FXaaXaaXaaW (SEQ ID NO:4) would have adequate strength of interaction with hdm2 to displace an adequate numbers of the wild type full length p53 molecules, such that the activity of p53 is adequately induced, resulting in growth inhibition or apoptosis, in view of the following teaching in the art:

Bottger et al teach that no mdm2 binding phage could be isolated from hexapeptide library, and that hexapeptides cannot provide sufficient correctely spaced contact points to bind to the mdm2 binding pocket with high enough affinity (p.2144, second column, paragraph before last), and

Further, peptides of any amino acids in length, such as those having less than 10 amino acids, would not contain the consensus residues such as P at the position 1, and/or L at position 10, found in the phage motif PX**F**XDY**W**XXL, wherein such consensus residues are necessary for providing the strength of interaction with hdm2, similar to that found in the clone 12/1 (IP3), as taught by Bottger et al (p.2144, first column, first paragraph).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. Moreover, the claims encompass a method for inducing growth inhibition or apoptosis in "any cancer cells in which mdm2 is not overexpressed".

One cannot extrapolate the teaching in the specification to the scope of the claims. It is unpredictable that disruption of the binding of p53 and mdm2 would induce growth inhibition or apoptosis in any cancer cells in which mdm2 is not overexpressed, because different cancer cells are different, and in some cancer cells, such as in Hela cells, Mdm2 does not block the apoptotic activity of p53 (Haup et al, of record, p.1600, second column, last paragraph). Haup et al teach that different genes may be repressed through interaction of p53, a transcriptional factor, with different components of the transcriptional machinery other than mdm2, and that some critical transcriptional factors in certain cancer cells may be bound by p53 through sites that are not blocked by mdm2 (Haup et al, of record, p.1603, second full paragraph). Thus one cannot predict that blocking the binding of p53 to mdm2 would necessary affect activity of p53 over growth inhibition or apoptosis.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

4. If Applicant could overcome the above 112, first paragraph, Claims 3, 11 are still rejected under 112, first paragraph for lack of enablement for " a portion" of p53 that is necessary for mdm2 binding or has at least 70% amino acid

sequence identity with the peptide of less than 25 amino acids in length, and including the peptide motif FxaaXaaXaaW (SEQ ID NO:4).

The specification discloses only a single fragment of p53, the sequence comprising amino acid residues 13-41 of wild type p53, that is necessary for mdm2 binding (p.2, lines 7-11).

It is noted that "a portion of human p53 which have the property of binding to mdm2" encompasses any portion or fragment within p53 that has the property of binding to mdm2, other than the disclosed amino acid residues 13-41 of wild type p53

Further, the specification only discloses only a single fragment of human p53, the amino acid sequence comprising SEQ ID NO:2 (p13 to N29) or residues 13-41 of wild type p53, wherein said fragment has at least 70% amino acid sequence identity with the peptide of less than 25 amino acids in length, and including the peptide motif FxaaXaaXaaW (SEQ ID NO:4) (figure 1 legend on page 24).

It is noted that " a portion of human p53" in claim 11 encompasses any portion or fragment within human p53, and it is not clear which portion of human p53 is referred to.

The specification does not teach which fragments of p53, other than the sequence comprising amino acid residues 13-29 or 13-41 of wild type p53, would have the peptide motif of SEQ ID NO:4.

Except for the sequence comprising amino acid residues 13-29 or 13-41 of wild type p53, **one cannot predict that "there exists other fragment(s) within p53" that is necessary for mdm2 binding or has at least 70% amino acid sequence identity with the peptide of less than 25 amino acids in length, and including the peptide**

motif FxaaXaaXaaW (SEQ ID NO:4), because not any peptide would have the property of binding to mdm2 or having at least 70% amino acid sequence identity with the peptide of less than 25 amino acids in length, and including the peptide motif FxaaXaaXaaW (SEQ ID NO:4).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

February 12, 2005